IN THE UNITED STATES PATENT OFFICE

#4

Application Serial No. 09/465,338 Our Ref.: PT1817

Filing Date: December 17, 1999

Applicant : BIOVAIL LABORATORIES INCORPORATED

Agent: Ivor M. Hughes, 175 Commerce Valley Drive West, Suite 200, Thornhill, Ontario Canada L3T 7P6

Title : CHRONOTHERAPEUTIC FORMULATIONS OF DILTIAZEM AND THE ADMINISTRATION THEREOF

Inventors : Kenneth Stephen Albert
Paul José Maes

TRANSMITTAL OF PETITION TO MAKE SPECIAL
Under 37 C.F.R. 1.102(d) and in Compliance with M.P.E.P. 708.02 VIII

March 24, 2000

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia 22202 U.S.A.

Dear Sir:

Attached is a Petition to Make Special Under 37 C.F.R. 1.102(d) and in Compliance with M.P.E.P. 708.02 VIII in the above-identified application.

Favorable consideration hereof is earnestly solicited.

Respectfully submitted,

IVOR M. HUGHES

Ivor M. Hughes
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Agent for Applicant

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Registration #37,015
Agent for Applicant

MKS*kdk
Enclosures

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The Commissioner of Patents
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2011 South Clark Place
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Dear Sir:

Applicant petitions the Commissioner to make special the above-captioned patent application. The basis for this petition is 37 C.F.R. 1.102(d). This petition is being submitted in compliance with M.P.E.P. 708.02 VIII and satisfies all of the requirements set forth therein, as described below. The instant application is a new application, i.e., it has not received any examination.

(a) This petition is being made in writing and is accompanied by the requisite fee of $130.00 U.S. funds for filing this Petition. If there is any deficiency or surplusage of the fees enclosed for the Petition, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

(b) All claims are directed to a single invention. If a restriction requirement is made, Applicant will make an election without traverse.

(c)1. *Foreign Patent Office searches*

Searches were prepared by the European Patent Office in connection with examination of this patent application. A copy of the search report is enclosed herein. The search report specifically identifies United States Application No. 465,338 and Canadian Application Serial No. 2,292,247, filed December 10, 1999, from which this United States application claimed priority.

Applicant respectfully submit that these searches satisfy the requirements described at M.P.E.P. 708.02(VIII)(c)

(d)1. *Foreign Patent Office searches*

With respect to the foreign patent office searches, the following references were cited in the searches:

EP 0856313 A
WO 93/00093 A

WO 93/09767 A
EP 0605174 A
EP 0282698 A
Zahirul, M. et al., "Recent Trends and Progress in Substained or Controlled Oral Delivery of Some Water Soluble Drugs: Morphine Salts, Diltiazem and Captopril", Drug Development and Industrial Pharmacy, US, New York, NY, vol. 21, no. 9, 1 January 1995, pages 1037-1070
Thiffault, Jean et al., "The influence of time of administration on the pharmacokinetics of a once-a-day diltiazem formulation: morning against bedtime", Biopharm. Drug Dispos., (1996), 17(2), 107-15

(d)3. *Other References and Information*

Applicant is aware of additional references that disclose various research studies using diltiazem. These references and studies are cited and discussed in the attached Information Disclosure Statement, along with references uncovered in searches carried out by Applicant.

(e) Applicant hereinbelow set out a detailed discussion of references which are closely related to the subject matter encompassed by the claims and which discussion points out how the claimed subject matter is patentable over each of the references.

Administration Time - Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hypertension Patients, Isao Kohno et al. (Chronobiology International 14(1), 71-84, (1997.) In the report of the study, Herbesser R™ (200mg) was identified as the Diltiazem preparation. Herbesser R™ is a Diltiazem formulation comprising a mixture of immediate release diltiazem - containing microspheres and sustained release diltiazem - containing coated microspheres. According to the

report, following a single dose (200 mg) administration, the time of peak plasma diltiazem concentration occurred at 12.5 hours after administration. The peak plasma diltiazem concentration Cmax in the persons studied was 107mg/ml. Following multiple dosages of 200 mg Diltiazem given over 7 days, the time of peak plasma diltiazem concentration (Cmax) was at 10 hours after administration. Cmax was 154 mg/ml.

However a careful review of the report shows inconsistencies which cannot support the authors' conclusions. Particularly at page 80, the best results shown in the graph are with respect to morning treatment with this formulation. Moreover at page 82, the authors themselves acknowledge the study cannot lead to reliable conclusions "because the number of patients was too small". Further, an immediate release portion of the dosage in the order of 15% is not desirable for evening administration. When the blood pressure is naturally at its lowest, not only is there no need for further reduction at that time, but such reduction can harm the patient. Particularly, if the blood pressure is reduced below a minimum the patient is put at a greater risk for cardiovascular accidents including stroke. Further, the 15% immediate release diltiazem is no longer available when needed. This reference does not teach or infer the invention as claimed.

In *A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets,* O. R.

Leeuwenkamp et al., Eur. J. Clin. Pharmacol (1994) 46:243-247, controlled release properties and relative systemic availabilities of two dosages of the same controlled release diltiazem tablet formulation were studied by comparing them as steady state with those of an immediate release formulation. In the testing, the diltiazem plasma concentration increased slowly from about 6 hours after the evening dose of both CR tablets (Diltiazem CR 90mg and Diltiazem CR 120 mg) resulting in relatively high plasma concentrations in the early morning hours. The clinicians concluded that twice-daily treatment with diltiazem CR tablets can replace thrice-daily treatment with a conventional diltiazem IR tablet. According to the clinicians "The early morning rise of the diltiazem plasma concentration, which might lead to a lower incidence of ischemic events, may be an important clinical advantage of both CR tablets."

On April 22, 1998, Searle Canada announced that its Chronovera (R) (controlled onset extended-release verapamil) a high blood pressure medication was now available in Canada. Chronovera (R) was, according to Searle Canada, specifically designed to work with the body's natural circadian variations and was designed to be taken once-a-day just before bedtime. Chronovera provided 24-hour blood pressure control but was designed to deliver peak concentrations of verapamil in the morning when the blood pressure, heart rate and incidence of cardiovascular events were highest. According to Searle Canada, simply changing the time you take the drug your physician has prescribed will not provide the same safety and effectiveness that is designed specially for chronotherapy using

verapamil. According to Searle Canada, its Chronovera (R) is unlike traditional medications including extended-release (XL) and sustained-release (SR) formulations which are usually prescribed in doses that maintain relatively constant levels of the drug in the body over a 24-hour period or attempt to maintain relatively constant levels of the drug in the body over a 24-hour period. According to Searle Canada, the prior formulations do not take into account the natural circadian variations in the body's physiological functions.

Sustained-release, once-daily diltiazem formulations have been taught which may be considered the traditional medication (according to Searle Canada). They appear not to give the benefits meant to be achieved by chronotherapy.

For example, in *Pharmacokinetic Properties and Antihypertensive Efficacy of Once-Daily Diltiazem*, J. G. Kelly et al., Journal of Cardio-Vascular Pharmacology, 17:6:957-963, (1991), the controlled-release formulation of diltiazem released a proportion of the diltiazem relatively rapidly with the remainder released over a period extending to 24-hours. During *in vitro* dissolution testing 15% of the diltiazem in the dosage form was released in the first two hours, 54% was released in the first six hours, 89% in the first 13 hours and all of the remainder was released between 13 and 24 hours after administration. The diltiazem capsules contained either 120 mg or 240 mg of diltiazem. It should be noted that no difference is shown

between the placebo and dosages in the article at wake-up (between 5:00 a.m. and 8:00 a.m.).

U.S. Patent 4,960,596 discloses slow release 12 hour diltiazem formulations whose dissolution, when measured in accordance with United States Pharmacopoeia 21, purports to be within broad limits (between 5% and 35% after one hour, between 15% and 40% after two hours, between 20% and 50% after three hours, between 30% and 75% after four hours, between 40% and 80% after six hours and between 55% and 95% after eight hours). The examples in the patent, however, provide more specific range limitations specifying range limitations for the formulations exemplified such as at column 4, lines 8-10 and column 5, lines 60-62. In the first series of examples the release into aqueous medium was measured using the method of USP No. 21 of 10%-20% after one hour, 30%-35% after four hours and 60%-75% after eight hours. In the later examples, the release into aqueous medium was measured using the method of USP No. 21 at 15%-35% after one hour, 55%-75% after four hours, 75%-95% after eight hours. These formulations were, however, twice a day (b.i.d.) formulations.

A series of patents have issued to Elan Corporation p.l.c. involving controlled absorption diltiazem pellet formulations for oral administration in which each pellet has a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with a specified organic acid covered by an outer membrane which permits release of

diltiazem from aqueous medium in accordance with U.S. Pharmacopoeia XX (Paddle Method) in buffered media at pH 1.5, pH 4.0 and pH 7.0. These are U.S. Patent 4,721,619; 4,891,230; 4,894,240; 4,917,899; (5,002,776; 5,219,621; 5,336,504; which are in the patent family of EP 0856313 cited in the European Patent Office Search Report) 5,364,620 and 5,616,345.

In U.S. Patent 4,721,619, dissolution rates of the pellets of examples are found at column 4, lines 41-49 and column 5, lines 5-12. The formulations, however are for 12 hour. The formulations of U.S. Patents 4,891,230 are also for administration every 12 hours.

U.S. Patent 4,894,240 purports to provide formulations for once-daily administration and specifies a general dissolution pattern at column 2, lines 43-52 and a more restricted dissolution pattern at column 3, lines 3-12. The dissolution rates are determined according to U.S. Pharmacopoeia XXI in 0.05M KCl at pH 7.0 and at 100 r.p.m. The examples of the patent, however, provide a more limited dissolution pattern under U.S. Pharmacopoeia XXI (Paddle Method) at column 7, lines 30-34 and 47-51, at column 8, lines 16-20, 32-36 and 49-53 and at column 8, line 66 - column 9, line 5. Similar examples are provided at columns 9, 10, 11 and 12. Nothing is taught with respect to formulations suitable as chronotherapeutics.

U.S. Patents 4,917,899, 5,364,620 and 5,616,345 are to the same effect. So are the remaining Elan patents, namely United States Patent Nos. 5,002,776,

5,219,621 and 5,336,504. Nothing in these patents teach formulations suitable as chronotherapeutics.

U.S. Patents 5,529,790, 5,376,384 and 5,478,573 which are in the patent family of EP 0605174 cited in the European Patent Office Search Report, purport to teach a delayed sustained-release pharmaceutical preparation in which a water-soluble drug core is surrounded by a hydratable diffusion barrier which delays drug release for about two to ten hours. While diltiazem hydrochloride dissolution patterns were provided in accordance with the U.S.P. basket dissolution method specified, no Cmax or the timing of the maximum blood levels is provided. The dissolution rates of the active are not appropriate for a suitable chronotherapeutic.

U.S. Patents 5,288,505 and 5,529,791 which are in the patent family of WO 93/00093 cited in the European Patent Office Search Report relate to extended-release galenical formulations of diltiazem or pharmaceutically acceptable salts thereof which comprise beads in which the active ingredient is in association with a wetting agent and which beads are coated by a microporous membrane. The Cmax of some formulations given in the patents provide for a Cmax after about 8-12 hours. Where the dosing of the formulations of the patents yields maximum diltiazem blood plasma levels (Cmax) of about 145 ng/ml, the Cmax is at about or less than 8 hours.

The applicants are also aware of a formulation marketed under the trade mark Tiazac™ a diltiazem HCl 24-hour sustained-release formulation based on teachings of U.S. Patent 5,529,791 and 5,288,505.

Following chronic administration of Tiazac (240 mg once daily), the average peak plasma Diltiazem concentration (Cmax) is 183 ng/ml (multiple dosage) which occurred after about 7 hours past dose administration. Tiazac™ provides a bioavailability of approximately 59% of the total Diltiazem in the first 12 hours and 41% in the second 12 hours (after 12 hours, 59%; after 16 hours 77% and after 20 hours 90%).

WO 93/09767, cited in the European Patent Office Search Report, (of which United States Patent No. 5,229,135 is a patent family member) teaches a sustained release diltiazem formulation for once daily administration. However, there is no discussion regarding chronotherapeutic application or a Cmax at the times included in the present application.

EP 0282698, cited in the European Patent Office Search Report, (of which United States Patent No. 5,622,716 is a patent family member) describes a process for preparing a retard diltiazem product for once a day administration. However, there is no reference or inference to chronotherapeutic application.

In an article entitled *Effect of Morning Versus Evening Dosing of Diltiazem on Myocardial Ischemia Detected by Ambulatory Electrocardiographic Monitoring in Chronic Stable Angio Pectoris,* PRA KASH, C. Deedwanian et al., The American Journal of Cardiology, Vol. 80, Aug. 15, 1997, p. 421-425, the authors compare a.m. and p.m. dosing without using an appropriate dosage form for p.m. The Tmax is achieved between 2-6 hours at steady state.

In an article *The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morning Against Bedtime,* Jean Thiffault et al., Biopharmaceutics & Drug Disposition, Vol. 17, 107 - 115 (1996), the once-a-day diltiazem formulation given at 2200 hours for seven days gave "significantly higher plasma concentrations of diltiazem in the early morning hours when the incidence of cardiovascular events is higher". The diltiazem dosages comprise 240 mg taken at 10:00 p.m. (22:00 hours) and maximum concentrations (Cmax) were achieved of 120 ng/ml after about six - eight hours of dosing. Unfortunately, the proposed system covers the period from 2:00 a.m. to 8:00 a.m. To be a true chronotherapeutic, the time period covered should be between about 6:00 a.m. and noon. Moreover, this formulation when given at night leads to significantly lower bioavailability than if given in the morning.

In an article *Recent Trends and Progress in Substained or Controlled Oral Delivery of Some Water Soluble Drugs: Morphine Salts, Diltiazem and*

Captopril, Zahirul, M. et al., Drug Development and Industrial Pharmacy, US, New York, NY, vol. 21, no. 9, 1 January 1995, pages 1037-1070, there is a discussion on the various technologies available for sustained and controlled release Diltiazem. There is no discussion relating to chronotherapeutics and application thereto.

Each and all of the above references do not include all of the elements of the claims of the present invention, namely, a controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.

In view of the above, Applicant respectfully requests grant of this petition to make special.

Respectfully submitted,

IVOR M. HUGHES

Ivor M. Hughes
Registration #27,759
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